CW

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/435, 31/44, 31/41, 31/415, 31/40, 31/35, 31/21

A1

(11) International Publication Number: WO 95/06470

(43) International Publication Date: 9 March 1995 (09.03.95)

(21) International Application Number: PCT/US94/07518

(22) International Filing Date: 5 July 1994 (05.07.94)

(30) Priority Data:

113,880	30 August 1993 (30.08.93)	US
114,270	30 August 1993 (30.08.93)	US

(60) Parent Applications or Grants
(63) Related by Continuation
US 113,880 (CIP)
Filed on 30 August 1993 (30.08.93)
US 114,270 (CIP)
Filed on 30 August 1993 (30.08.93)

(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SCOLNICK, Edward, M. [US/US]; 811 Wickfield Road, Wynnewood, PA 19096 (US).

(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract

The present invention relates to the administration of an HMG-CoA reductase inhibitor, including lovastatin (MEVACOR®) and simvastatin (ZOCOR®), the open-ring dihydroxy acid forms thereof, and salts and esters thereof, and pravastatin (PRAVACHOL®) and fluvastatin (LESCOL®), the closed ring lactone forms and salts and esters thereof, to humans to lower Apolipoprotein E isoform 4 (ApoE isoform 4) levels in the central nervous system to treat, arrest the development of and prevent the onset of Alzheimer's disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

TITLE OF THE INVENTION

PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

SUMMARY OF THE INVENTION

The present invention relates to the administration of an HMG-CoA reductase inhibitor, including lovastatin (MEVACOR®) and simvastatin (ZOCOR®), the open-ring dihydroxy acid forms thereof, and salts and esters thereof, and pravastatin (PRAVACHOL®) and fluvastatin (LESCOL®), the closed ring lactone forms and salts and esters thereof, to humans to lower Apolipoprotein E isoform 4 (ApoE isoform 4) levels in the central nervous system to treat, arrest the development of and prevent the onset of Alzheimer's disease.

BACKGROUND OF THE INVENTION

Alzheimer's disease is a neurodegenerative disease of the brain leading to severely impaired cognition and functionality. This disease leads to progressive regression of memory and learned functions. Alzheimer's disease is a complex disease that affects cholinergic neurons, as well as serotonergic, noradrenergic and other central neurotransmitter systems. Manifestations of Alzheimer's disease extend beyond memory loss and include personality changes, neuromuscular changes, seizures, and occasionally psychotic features.

Alzheimer's disease is the most common type of dementia in the United States. Some estimates suggest that up to 47% of those older than 85 years have Alzheimer's disease. Since the average age of the population is on the increase, the frequency of Alzheimer's disease is increasing and requires urgent attention. Alzheimer's is a difficult medical problem because there are presently no adequate methods available for its prevention or treatment.

Three classes of drugs are being investigated for the treatment of Alzheimer's disease. The first class consists of compounds that augment acetylcholine neurotransmitter function. Currently, cholinergic agonists such as the anticholinesterase drugs are being used in the treatment of Alzheimer's disease. In particular, physostigmine

(eserine), an inhibitor of acetylcholinesterase, has been used in its treatment. The administration of physostigmine has the drawback of being considerably limited by its short half-life of effect, poor oral bioavailability, and severe dose-limiting side-effects, particularly towards the digestive system. Tacrine (tetrahydroaminocridine) is another cholinesterase inhibitor that has been employed; however, this compound may cause hepatotoxicity.

A second class of drugs that are being investigated for the treatment of Alzheimer's disease is neurotropics that affect neuron metabolism with little effect elsewhere. These drugs improve nerve cell function by increasing neuron metabolic activity. Piracetam is a neurotropic that may be useful in combination with acetylcholine precursors and may benefit Alzheimer's patients who retain some quantity of functional acetylcholine neurons. Oxiracetam is another related drug that has been investigated for Alzheimer treatment.

A third class of drugs include those drugs that affect brain vasculature. A mixture of ergoloid mesylates is used for the treatment of dementia. Ergoloid mesylates decrease vascular resistance and thereby increase cerebral blood flow. Also employed are calcium channel blocking drugs including Nimodipine which is a selective calcium channel blocker that affects primarily brain vasculature.

Other miscellaneous drugs are targeted to modify other defects found in Alzheimer's disease. Selegiline, a monoamine oxidase B inhibitor which increases brain dopamine and norepinephrine has reportedly caused mild improvement in some Alzheimer's patients. Aluminum chelating agents have been of interest to those who believe Alzheimer's disease is due to aluminum toxicity. Drugs that affect behavior, including neuroleptics, and anxiolytics have been employed. Side effects of neuroleptics range from drowsiness and anti cholinergic effects to extrapyramidal side effects; other side effects of these drugs include seizures, inappropriate secretion of antidiuretic hormone, jaundice, weight gain and increased confusion. Anxiolytics, which are mild tranquilizers, are less effective than neuroleptics, but also have

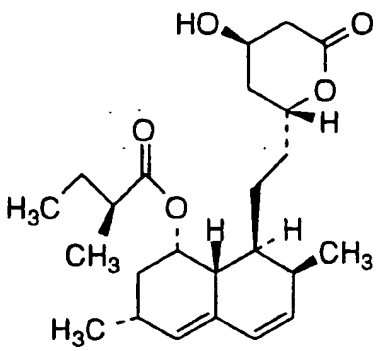
milder side effects. Use of these behavior-affecting drugs, however, remains controversial.

None of the drugs discussed above are targeted to prevent the onset of Alzheimer's disease. These drugs are employed as treatments for the disease. At best one or more of these drugs may slow down the course of the disease, but there is currently no evidence for this.

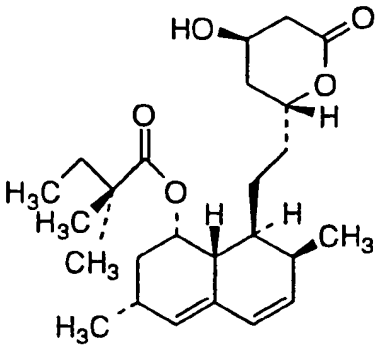
Recently, it has been reported in Corder et al., "Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families," *Science* **261**:921-23 (13 August 1993), that the Apolipoprotein E type 4 allele ("APOE-ε4") is genetically associated with the common late onset familial and sporadic forms of Alzheimer's disease. Specifically, it was found that the risk of Alzheimer's disease increased by a factor of 2.84 for each additional Apolipoprotein E type 4 allele the patient had. Hence, individuals with two copies of the Apoliprotein E type 4 allele were more than eight times as likely to be affected with Alzheimer's disease than individuals who did not possess any copies of the Apolipoprotein E type 4 allele. The protein encoded by Apolipoprotein E type 4 allele, ApoE isoform 4, has a higher avidity *in vitro* for β–amyloid than ApoE isoform 3. Apolipoprotein E is the major apolipoprotein in the central nervous system, where it appears to be involved in nerve regeneration following injury. Apolipoprotein E is synthesized in several extra hepatic tissues, including brain, and is catabolized predominantly by the liver.

The present invention provides for a method of treating, arresting the development of and preventing Alzheimer's disease by regulating the amount of ApoE isoform 4 circulating in the bloodstream and in the brain, most particularly in the brain of a patient with or at risk of developing Alzheimer's disease employing an HMG-CoA reductase inhibitor selected from lovastatin and simvastatin, including the corresponding open-ring dihydroxy acid forms and the salts and esters thereof.

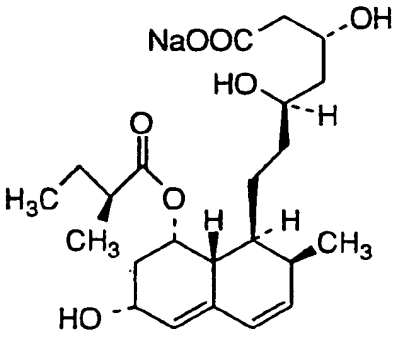
Lovastatin (MEVACOR®), simvastatin (ZOCOR®) pravastatin (PRAVACHOL®), and fluvastatin (LESCOL®) are known cholesterol lowering agents.



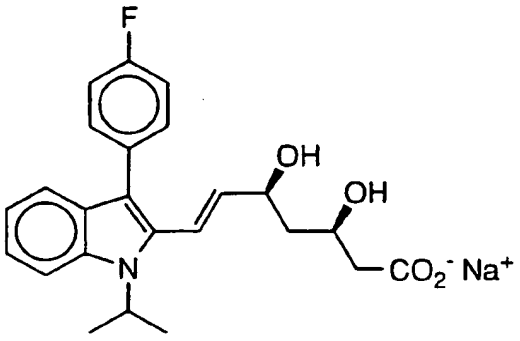
LOVASTATIN



SIMVASTATIN



PRAVASTATIN



FLUVASTATIN

These compounds are inhibitors of HMG-CoA reductase, which is the rate-limiting step in the biosynthesis of cholesterol.

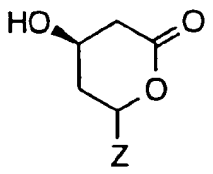
Lovastatin and related compounds are disclosed in U.S. Patent No. 4,231,938; simvastatin and related comounds are disclosed in U.S. Patent No. 4,450,171 and U.S. Patent No. 4,346,227; pravastatin and related compounds are disclosed in U.S. Patent No. 4,346,227 and fluvastatin and related compounds such as disclosed in PCT Publication WO 84/02131.

The present invention provides for a method of preventing and treating Alzheimer's disease by treating a patient in need of such

treatment with an HMG-CoA reductase inhibitor, including lovastatin (MEVACOR®) and simvastatin (ZOCOR®), the open-ring dihydroxy acid forms thereof, and salts and esters thereof, and pravastatin (PRAVACHOL®) and fluvastatin (LESCOL®), the closed ring lactone forms and salts and esters thereof, to lower Apolipoprotein E isoform 4 (ApoE isoform 4) levels in the central nervous system.

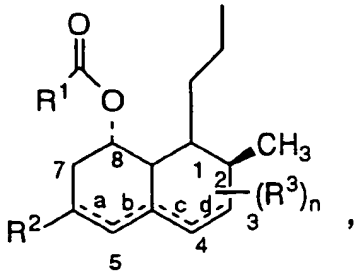
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to administration of an HMG-CoA reductase inhibitor to humans at risk for developing Alzheimer's disease for the purpose of preventing the onset of Alzheimer's disease. The HMG-Co A reductase inhibitors which are used in the method of this invention include the compounds represented by the following structural formula (I):



(I)

wherein:
Z is selected from:

(a) 

wherein:
R^1 is C_{1-10}alkyl,
R^2 is selected from:

(a) hydrogen,

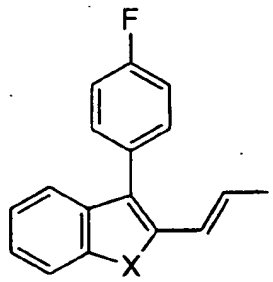
(b) C_{1-3} alkyl,
(c) hydroxy, and
(d) C_{1-3} alkyl substituted with hydroxy;

R^3 is selected from:
(a) C_{1-3} alkyl,
(b) hydroxy,
(c) oxo, and
(d) C_{1-3} alkyl substituted with hydroxy;

n is 0,1,or 2;

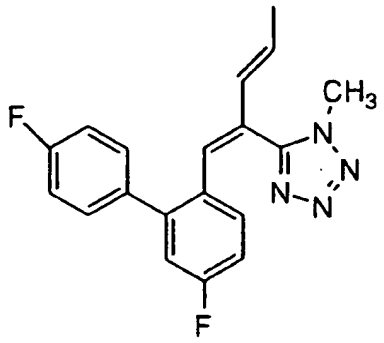
a, b, c and d are all single bonds or a and c are double bonds or b and d are double bonds or one of a, b, c or d is a double bond;

(b)

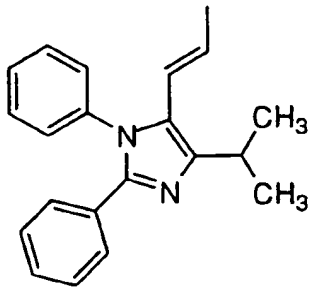


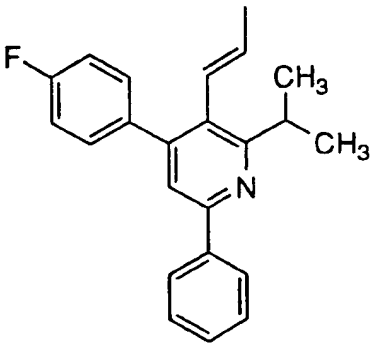
wherein X is $NCH(CH_3)_2$ or $C(CH_2)_4$;

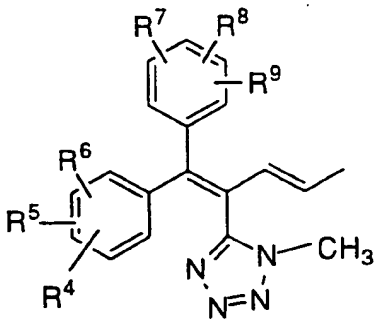
(c)



;

(d) 

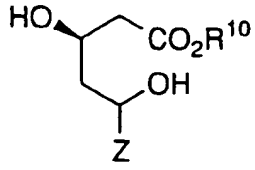
(e) 

(f) 

wherein R^4 and R^9 are each independently selected from hydrogen, halogen, C1-4 alkyl, C1-4 alkoxy and trifluoromethyl, and R^5, R^6, R^7, and R^8 are each independently selected from hydrogen, halogen, C1-4 alkyl, and C1-4 alkoxy;
the corresponding open-ring dihydroxy acid forms thereof and pharmaceutically acceptable salts and esters thereof.

The terms "halo" and "halogen" each refer to -F, -Cl, -Br and -I.

The term "open-ring dihydroxy acid form and pharmaceutically acceptable salts and esters" of the compound of formula (I) refers to the corresponding compound of formula (II) below:



(II)

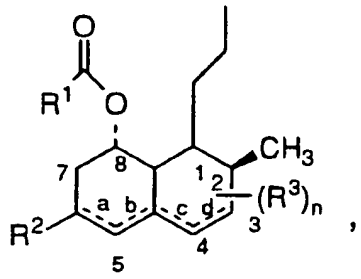
wherein R^{10} is selected from:

(a) hydrogen,
(b) C_{1-5}alkyl,
(c) substituted C_{1-5}alkyl in which the substituent is selected from the group consisting of:
  (1) phenyl,
  (2) dimethylamino, and
  (3) acetylamino, and
(d) 2,3-dihydroxypropyl;

and pharmaceutically acceptable salts thereof.

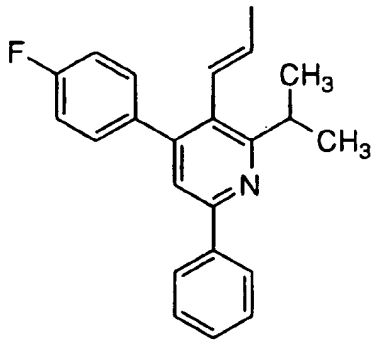
The pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethyl ammonium hydroxide. These salts are prepared by standard procedures.

One class of compounds of the present invention are those wherein Z is:

(a) 

and n is 1. One subclass of these compounds is where R^3 is 5-OH, and a, b, c, and d are each single bonds. Another subclass of compounds is characterized by R^3 being 3-oxo and a and c being a double bond, or c being a double bond. Yet a third subclass of these compounds is where R^3 is 7-(1-hydroxyethyl), b and d are double bonds; provided that when R^2 is OH, b and d are double bonds or c is a double bond or a, b, c, and d are single bonds.

Another class of compounds of the present invention are those wherein Z is:



As used herein the term "preventing" includes not only preventing of the onset of the disease in disease-free patients, but also arresting the development of the disease in patients already manifesting symptoms of the disease, and ameliorating symptoms in patients afflicted with the disease.

Specifically, the method of this invention is useful for treating individuals who possess one or two copies of the apolipoprotein E type 4 allele. These individuals are more likely to develop late onset and sporadic Alzheimer's disease. The method of this invention is also

useful in halting the progression of Alzheimer's disease in a patient who already exhibits symptoms of dementia, and ameliorating the degenerative effects of Alzheimer's disease.

The present invention provides for a means of lowering the levels of Apolipoprotein E isoform 4 circulating in the bloodstream and in the brain by employing an HMG-CoA reductase inhibitor of structural formula (I) the open ring dihydroxy acid forms thereof and salts and esters thereof. Particularly, this invention relates to the lowering of Apolipoprotein E isoform 4 circulating through the central nervous system and present in the cerebrospinal fluid.

Apolipoprotein E isoform 4 ("ApoE isoform 4") is an apolipoprotein which is the gene product of the apolipoprotein E type 4 allele. Possession of one or two copies of the apolipoprotein E type 4 allele has been linked to a greatly increased risk of developing Alzheimer's disease. The present invention provides for a method of decreasing circulating blood levels of ApoE isoform 4 throughout the body, including the brain. In the liver, low density lipoprotein receptors (LDL receptors) are responsible for absorbing and taking up from the bloodstream various lipoproteins including some of those containing ApoE isoform 4. LDL receptors are regulated by gene repressors derived from cholesterol which suppress the transcription of the LDL-receptor. Inhibition of cholesterol biosynthesis reduces the presence of these cholesterol-derived LDL gene repressors. This relieves the suppression of the production of the LDL receptor, leading to production of additional LDL receptors in the liver, which, in turn, remove additional ApoE containing lipoproteins from the bloodstream. Reduced levels of ApoE isoform 4 in the bloodstream promotes an increase in the flux of ApoE isoform 4 from the CNS to the plasma, thus reducing the risk of, halting the development of and/or ameliorating the symptoms of Alzheimer's disease. It is also possible that these agents could work directly on the CNS to reduce ApoE levels in the brain.

For the prevention, treatment or amelioration of the symptoms of Alzheimer's disease, the HMG-CoA reductase inhibitor of structural formula (I), the open-ring dihydroxy acid forms thereof, and

salts and esters thereof, may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers. It is usually desirable to use the oral route. The compounds of structural formula (I), the open-ring dihydroxy acid forms thereof, and salts and esters thereof, may be administered orally in the form of a capsule, a tablet or the like. The orally administered medicament may be administered in the form of a time-controlled release vehicle, including diffusion controlled systems, osmotic devices, dissolution controlled matrices and erodible/degradable matrices. Doses may be varied, depending on the age, severity, body weight and other conditions of human patients, but daily dosage for adults is within a range of from about 1 mg to 1000 mg (preferably 5 to 100 mg,) which may be given in a single dose or in two to four divided doses. Higher doses may be favorably employed as required.

The following example is given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

EXAMPLE 1

Apolipoprotein E Polymorphism On ApoE Response To an HMG-CoA Reductase Inhibitor

Method: One hundred eleven outpatients with moderate hypercholesterolemia were treated at five lipid clinics with the National Cholesterol Education Program Step 2 diet (which is low in fat and cholesterol) and lovastatin (20 mg once a day), both alone and together. A diet high in fat and cholesterol and a placebo identical n appearance to the lovastatin were used as the respective controls. Each of the 97 patients completing the study (58 men and 39 women) underwent four consecutive nine-week periods of treatment according to a randomized, balanced design: a high fat diet--placebo period, a low-fat diet--placebo period, a high-fat diet--lovastatin period, and a low-fat diet--lovastatin period.

Mean ApoE levels at the End of Each Intervention

Apo E phenotype (n)	HF/P	LF/P	HF/L	LF/L	p(diet)	p(drug)
3/3(52)	7.5	7.4	6.9	6.5	0.07	<0.001
3/4(26)	6.9	6.2	5.4	5.4	0.17	<0.001
4/4(5)	8.9	8.0	4.0	5.8	n too small	n too small

HF=high fat; LF= low fat; P=placebo; L=lovastatin; ApoE unit is mg/dl.

There is considerable variation of ApoE within and between patients. (This is true of other components of VLDL, including VLDL cholesterol and triglycerides.) Also, the sample sizes for the 4/4 and 3/4 phenotypes are relatively small. For these reasons, % change in the mean, (rather than mean or median % change is shown below:

% Change in Mean ApoE

phenotype (n)	due to diet	due to drug
3/3 (52	-5	-11
3/4 (26)	-7	-21
4/4	+7	-42

These data suggest that the serum level of ApoE isoform 4 falls more during treatment with lovastatin, an HMG-CoA reductase inhibitor, than does the level of ApoE isoform 3.

EXAMPLE 2

Effect of HMG-CoA Reductase Inhibitor on Cerebrospinal Fluid Levels of ApoE in Alzheimer's Patients Homozygous for ApoE Type 4 Allele

The following protocol is used to determine the effect of HMG-CoA reductase inhibitors on cerebrospinal fluid levels of ApoE in Alzheimer's patients homozygous for ApoE type 4 allele. Other HMG-CoA reductase inhibitors may be substituted for simvastatin.

A randomized, double-blind placebo controlled, parallel-design, multicenter six week study is conducted. Approximately 30 men and women (to provide 20 patients with baseline and follow-up lumbar punctures) between the ages of 50 and 85 years with a diagnosis of sporadic or late-onset familial AD, homozygous for the ApoE4 isoform, and with a low density lipoprotein (LDL) cholesterol level greater than 100 mg/dl are recruited for participation in the study and informed consent is obtained. (Patients incapable of giving informed consent have written consent from their guardian or representative.)

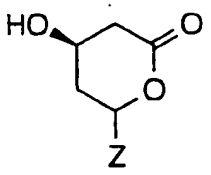
Patients qualifying for entry after screening are randomized to simvastatin, 40 mg/day or placebo for six weeks. A lumbar puncture will be performed prior to randomization and at Week 6 to determine cerebrospinal fluid levels of ApoE and other apolipoproteins. If the lumber puncture is judged traumatic (greater than grossly hemorrhage and greater than 50,000 RBC/mm^3F), it is repeated in one week. Plasma is obtained at these time points for plasma total, LDL, HDL cholesterol and apolipoproteins including ApoE. For those patients in whom the six week lumbar puncture follow-up cannot be performed on time, a two week window is allowed (Week 4 to 8 of active treatment). The primary endpoint is a comparison between simvastatin and placebo groups in the mean cerebrospinal ApoE levels.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

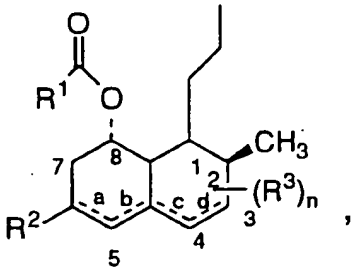
1. A method for preventing, treating, or ameliorating the symptoms of Alzheimer's disease in a human patient comprising administration to the patient of an HMG-CoA reductase inhibitor.

2. The method for preventing, treating, or ameliorating the symptoms of Alzheimer's disease in a human patient of Claim 1 comprising administration to the patient of an HMG-CoA reductase inhibitor of structural formula (I),



(I)

wherein:
Z is selected from:

(a) 

wherein:
R^1 is C_{1-10}alkyl,
R^2 is selected from:

(a) hydrogen,
(b) C_{1-3} alkyl,
(c) hydroxy, and
(d) C_{1-3} alkyl substituted with hydroxy;

R^3 is selected from:

(a) C_{1-3} alkyl,

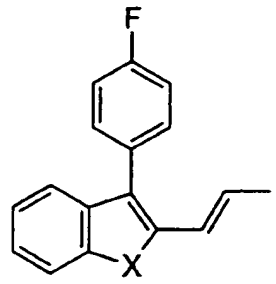
(b) hydroxy,

(c) oxo, and

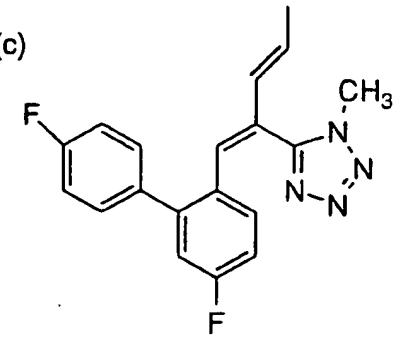
(d) C_{1-3} alkyl substituted with hydroxy;

n is 0,1,or 2;

a, b, c and d are all single bonds or a and c are double bonds or b and d are double bonds or one of a, b, c, or d is a double bond;

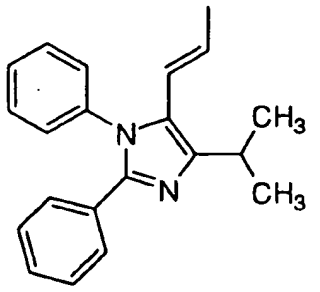
(b) 

wherein X is $NCH(CH_3)_2$ or $C(CH_2)_4$;

(c) 

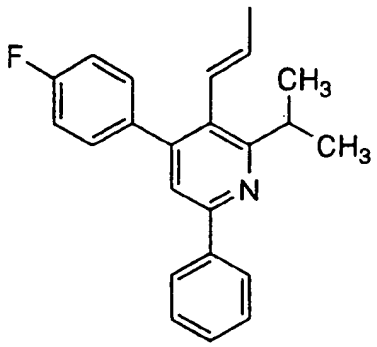
;

(d)



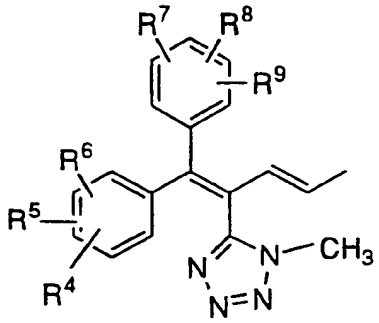
;

(e)



;

(f)



,

wherein R^4 and R^9 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy and trifluoromethyl, and R^5, R^6, R^7, and R^8 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

the corresponding open-ring dihydroxy acid forms thereof and pharmaceutically acceptable salts and esters thereof.

3. The method of Claim 1 wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin and fluvastatin.

4. The method of Claim 3 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

5. The method of Claim 1 wherein the patient has at least one copy of the Apolipoprotein E type 4 allele.

6. The method of Claim 1 wherein the patient has Alzheimer's disease.

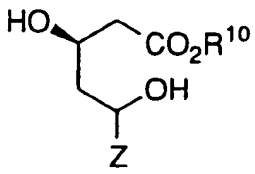
7. The method of Claim 1 wherein 1 to 1000 mg of the HMG-CoA reductase inhibitor is administered daily.

8. The method of Claim 7 wherein 5 to 100 mg of the HMG-CoA reductase inhibitor is administered daily.

9. The method of Claim 1 wherein the HMG-CoA reductase inhibitor is administered orally.

10. The method of Claim 7 wherein the HMG-CoA reductase inhibitor is administered by a controlled release dosage form.

11. The method of Claim 2 wherein the HMG-CoA reductase inhibitor is in the open ring dihydroxy acid form of formula (II):



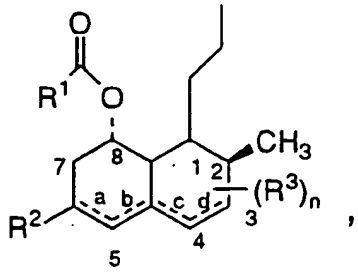
(II)

wherein R^{10} is selected from:

(a) hydrogen,
(b) C_{1-5}alkyl,
(c) substituted C_{1-5}alkyl in which the substituent is selected from the group consisting of:
  (1) phenyl,
  (2) dimethylamino, and
  (3) acetylamino, and
(d) 2,3-dihydroxypropyl;

and pharmaceutically acceptable salts thereof.

12. The method of Claim 2 wherein Z is:

(a) 

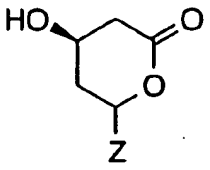
wherein:
n is 1 and

(1) R^3 is 5-OH, and a, b, c, and d are each single bonds,
(2) R^3 is 3-oxo and a and c are each double bonds, or c is a double bond, or
(3) R^3 is 7-(1-hydroxyethyl), and b and d are double bonds;

provided that when R^2 is OH, b and d are double bonds or c is a double bond or a, b, c, and d are single bonds.

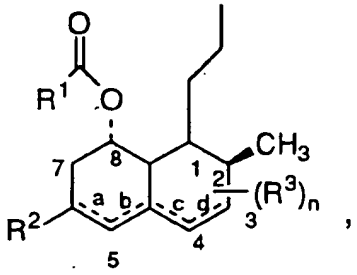
13. A method of lowering ApoE isoform 4 levels in the cerebrospinal fluid of a patient in need of such treatment comprising the administration to the patient of an HMG-CoA reductase inhibitor.

14. The method of lowering ApoE isoform 4 levels in the cerebrospinal fluid of the patient according to Claim 13 comprising administration to the patient of an HMG-CoA reductase inhibitor of structural formula (I),



(I)

wherein:
Z is selected from:

(a) 

wherein:
R^1 is C_{1-10}alkyl,
R^2 is selected from:

(a) hydrogen,
(b) C_{1-3} alkyl,
(c) hydroxy, and

(d) C_{1-3} alkyl substituted with hydroxy;

R^3 is selected from:

(a) C_{1-3} alkyl,

(b) hydroxy,

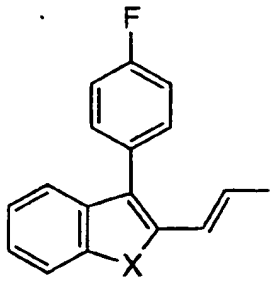
(c) oxo, and

(d) C_{1-3} alkyl substituted with hydroxy;

n is 0,1,or 2;

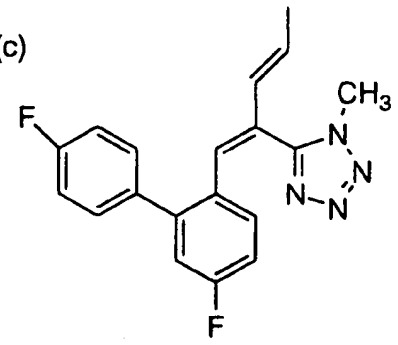
a, b, c and d are all single bonds or a and c are double bonds or b and d are double bonds or one of a, b, c, or d is a double bond;

(b)



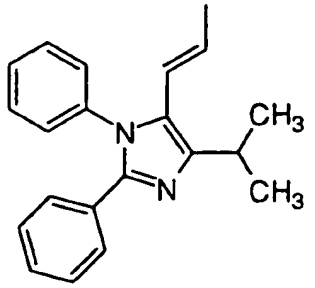
wherein X is $NCH(CH_3)_2$ or $C(CH_2)_4$;

(c)



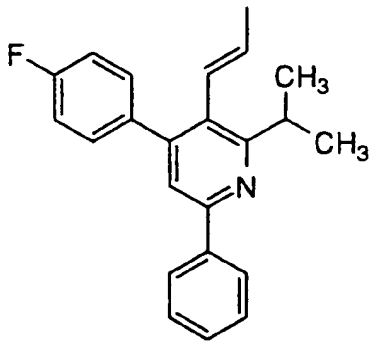
;

(d)



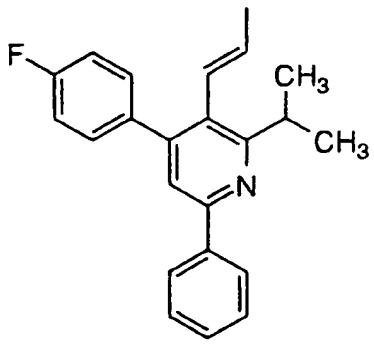
;

(e)



;

(e)



;

wherein R^4 and R^9 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy and trifluoromethyl, and R^5, R^6, R^7, and R^8 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

the corresponding open-ring dihydroxy acid forms thereof and pharmaceutically acceptable salts and esters thereof.

15. The method of Claim 13 wherein the HMG-CoA reductase inhibitor is selected from lovastatin, simvastatin, pravastatin and fluvastatin.

16. The method of Claim 15 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

17. The method of Claim 13 wherein the patient has at least one copy of the Apolipoprotein E type 4 allele.

18. The method of Claim 13 wherein the patient has Alzheimer's disease.

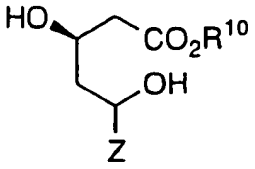
19. The method of Claim 13 wherein 1 to 1000 mg of the HMG-CoA reductase inhibitor is administered daily.

20. The method of Claim 19 wherein 5 to 100 mg of the HMG-CoA reductase inhibitor is administered daily.

21. The method of Claim 13 wherein the HMG-CoA reductase inhibitor is administered orally.

22. The method of Claim 13 wherein the HMG-CoA reductase inhibitor is administered by a controlled release dosage form.

23. The method of Claim 13 wherein the HMG-CoA reductase inhibitor is in the open ring dihydroxy acid form of formula (II):



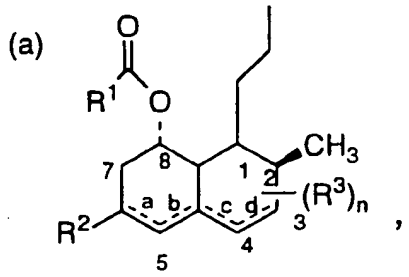
(II)

wherein R^{10} is selected from:

(a) hydrogen,
(b) C_{1-5}alkyl,
(c) substituted C_{1-5}alkyl in which the substituent is selected from the group consisting of:
  (1) phenyl,
  (2) dimethylamino, and
  (3) acetylamino, and
(d) 2,3-dihydroxypropyl;

and pharmaceutically acceptable salts thereof.

24. The method of Claim 2 wherein Z is:

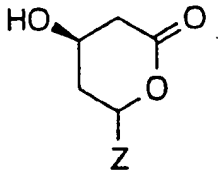


wherein:
n is 1 and

(1) R^3 is 5-OH, and a, b, c, and d are each single bonds,
(2) R^3 is 3-oxo and a and c are each double bonds, or c is a double bond, or
(3) R^3 is 7-(1-hydroxyethyl), and b and d are double bonds;

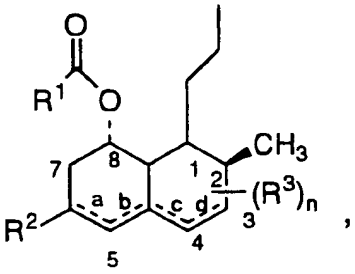
provided that when R^2 is OH, b and d are double bonds or c is a double bond or a, b, c, and d are single bonds.

25. A method of lowering ApoE isoform 4 levels in a patient in need of such treatment comprising the administration to the patient of an HMG-CoA reductase inhibitor of structural formula (I),



(I)

wherein:
Z is selected from:

(a) 

wherein:
R^1 is C_{1-10}alkyl,
R^2 is selected from:

(a) hydrogen,
(b) C_{1-3} alkyl,
(c) hydroxy, and
(d) C_{1-3} alkyl substituted with hydroxy;

R^3 is selected from:

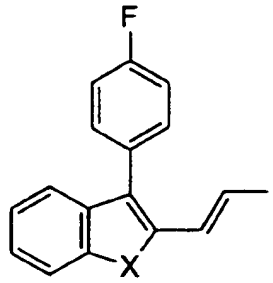
(a) C_{1-3} alkyl,
(b) hydroxy,
(c) oxo, and

(d) C_{1-3} alkyl substituted with hydroxy;

n is 0,1,or 2;

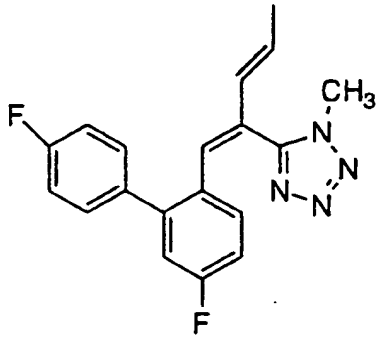
a, b, c and d are all single bonds or a and c are double bonds or b and d are double bonds or one of a, b, c, or d is a double bond;

(b)



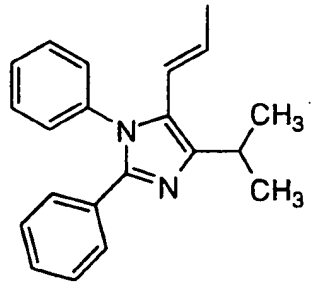
wherein X is $NCH(CH_3)_2$ or $C(CH_2)_4$;

(c)



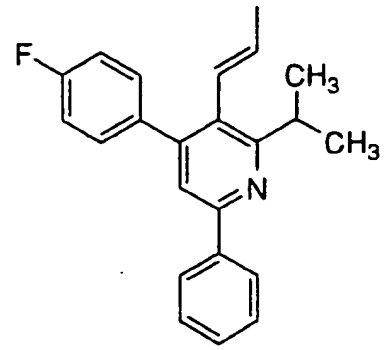
;

(d)

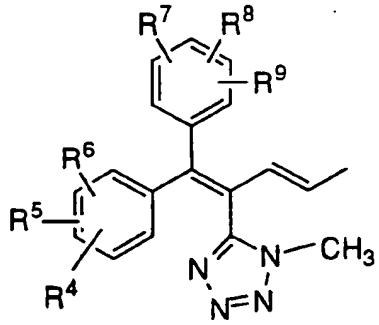


;

(e)



(f)



wherein R^4 and R^9 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy and trifluoromethyl, and R^5, R^6, R^7, and R^8 are each independently selected from hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

the corresponding open-ring dihydroxy acid forms thereof and pharmaceutically acceptable salts and esters thereof;

provided that when R^1 is 1-methyl propyl or 1,1-dimethylpropyl, R^3 is hydrogen and b and d represent double bonds, R^2 is not methyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07518

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/435, 31/44, 31/41, 31/415, 31/40, 31/35, 31/21
US CL : 514/277, 336, 381, 382, 396, 397, 414, 419, 459, 460, 510
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/277, 336, 381, 382, 396, 397, 414, 419, 459, 460, 510

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE, EMBASE: HMG CO-A REDUCTASE INHIBITOR, ALZHEIMER'S

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Chemical Abstracts, Volume 96, No. 23, issued 1982, Tobert et al., "Cholesterol-Lowering Effect of Mevinolin, an Inhibitor of 3-Hydroxy-methylglutaryl-coenzyme A Reductase, in Healthy Volunteers", abstract no. 193161s, J. Clin. Invest., 69(4), 913-19.	1,8,10 ---------- 1,3-11

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 21 OCTOBER 1994	Date of mailing of the international search report 27 OCT 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KIMBERLY JORDAN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07518

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-12

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07518

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-12, drawn to a method of preventing, treating, or ameliorating Alzheimer's disease by administering an HMG CoA reductase inhibitor.
Group II, claim(s) 13-25, drawn to a method of lowering ApoE isoform 4 levels by administering an HMG-CoA reductase inhibitor.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I and II above have lack of unity because each method is a separate medical condition and may be treated by separate methods. Thus each method is a special technical feature unrelated to the other. If technical features are unrelated there is a lack of unity (see MPEP AI-37, Example 10).